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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/689,430	10/12/2000	Christopher E. Walsh	35052/204373 (5052-53)	7095

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ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
LI, QIAN J	
ART UNIT	**PAPER NUMBER**
1632	19

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/689,430	WALSH ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,58-77,79-88 and 90-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,58-77,79-88 and 90-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed on March 11, 2003 has been entered and assigned as Paper #18. Claims 78 and 89 have been canceled. Claims 1, 9, 12, 18, 58-65, 68, 73-77, 79, 80, 82 have been amended. Claims 91 and 92 are newly submitted. Claims 1-20 58-77, 79-88, and 90-92 are pending and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION

The prior rejection of Claims 18, 19, 35, and 68-90 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is withdrawn in view of the response showing that the B-domain deleted factor VIII and its variants are well known in the art.

ENABLEMENT REQUIREMENT

The prior rejection of Claims 18, 19, 35, and 68-90 under this provision is withdrawn in light of the withdrawal of the rejection under WRITTEN DESCRIPTION REQUIREMENT.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 91 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 91 recites the limitation "the method of claim 1". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-11, 13-18, 20, 58-77, 79-88, and 90 stand rejected under 35 U.S.C. 103(a) as unpatentable over *Dwarki et al* (US 6,221,349), in view of *Robbins* (Pharmacol Ther 1998;80:35-47) and *Pittman et al* (Blood 1993;81:2925-35), and evidenced by *Vorachek et al* (J Bio Chem 2000 Sep;29031-41); the rejection applies to new claims 91 and 92.

New claims 91 and 92 add limitation of "capable of expressing B-domain deleted factor VIII at a level sufficient for treatment of a factor VIII associated-disorder" to previous vector claims.

In paper #18, applicants argue that the claims have been amended to recite that the only promoter driving expression of the nucleotide sequence encoding B-domain deleted factor VIII is an AAV ITR, whereas the prior art of record teach that the hFVIII is difficult to express, and the AAV ITR is an inefficient promoter, thus the skilled in the art believe that a gene therapy vector expressing hFVIII must contain a strong promoter. The response also cited several references of the record to support the argument.

The references and argument have been carefully considered but they are not persuasive for reasons of record and following.

Dwarki et al teach a rAAV selected from anyone of the AAV serotype 1-7 and comprising an AAV ITR (column 5, lines 3-4), wherein the vector could encode a factor VIII (column 9, line 44) operably linked to an AFP enhancer, (liver-specific enhancer, column 6, line 35). *Dwarki et al* do not teach that another promoter is required for efficiently expression of the protein of interest, such as FVIII, thus, the teaching of *Dwarki et al* still meet claim limitation.

With respect to the references submitted by applicants, *Chuah et al* (1998) teach the difficulties in FVIII production, however, the difficulties discussed are unrelated to the promoter function of an AAV vector, and *Chuah et al* suggest the resolution as to express high levels of FVIII in tissues that permit direct secretion of FVIII into the blood stream. *Ill et al* (1997) teach optimizing the expression of FVIII by using liver-specific

promoter and enhancer in general, which complement the teachings of *Dwarki et al*. *Zhang et al* do teach that AAV ITR has a very low transcriptional activity compared to conventional promoters often used to drive gene expression. However, they also teach that it has *not* been possible to incorporate an *additional* promoter with the gene of interest (CFTR, in this case) into the AAV vector because of the size limitation of AAV (2^{nd}-3^{rd} paragraphs, page 10159). Thus, they provided a strategy as reducing the size of CFTR cDNA and still use AAV ITR as the *sole* promoter for the rAAV-CFTR. This strategy is consistent with that of instant invention, thus, it only provides further evidence showing that it would have been obvious for the ordinary skilled in the art to apply the same principle in design an AAV for expressing a protein of interest, such as FVIII.

It is also noted that the intended use of a product, "a gene therapy vector" in the instant case, carries little weight in the determination of the novelty of a product claim. The MPEP states, "IN APPARATUS, ARTICLE, AND COMPOSITION CLAIMS, INTENDED USE MUST RESULT IN A STRUCTURAL DIFFERENCE BETWEEN THE CLAIMED INVENTION AND THE PRIOR ART IN ORDER TO PATENTABLY DISTINGUISH THE CLAIMED INVENTION FROM THE PRIOR ART." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02). Therefore, the rejection stands.

In paper #18, applicants further argue that *Dwarki et al* do not teach using B-domain-deleted FVIII, *Robbins et al and Pittman et al* do not teach that B-domain-deleted FVIII could be successfully expressed in an AAV vector at sufficient levels. Therefore, the Office has not established a *prima facie* case of obviousness.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, *Dwarki et al* teach a rAAV driven by an AAV ITR, they also teach a liver-specific enhancer that could be used in the vector. *Robbins et al* teach the size-limitation of an AAV vector, and *Pittman et al* teach the effectiveness in treating hemophilia A using B domain-deleted FVIII.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the vector and the expression control elements taught by *Dwarki et al and Robbins et al* in expressing FVIII, and reducing the length of the FVIII by deleting the B-domain of FVIII to meet the size limitation of an AAV, with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed vector because it is known that rAAV is well-suited for gene delivery but requires a smaller insertion size of heterologous sequences. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In response to applicant's argument that there is no suggestion to combine the references, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would

have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

For reasons of record and set forth above, the rejection stands.

Claim 12 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Dwarki et al* (US 6,221,349), *Robbins* (Pharmacol Ther 1998;80:35-47) and *Pittman et al* (Blood 1993;81:2925-35) as applied to claims 1, 3-11, 13-18, 20, 58-77, 79-88, and 90-92 above, and further in view of *ILL et al* (US 5,744,326).

Amended claim 12 is drawn to a particular liver specific enhancer having a nucleotide sequence given as about 150-278 of SEQ ID No: 1. The combined teachings of *Dwarki et al*, *Robbins,* and *Pittman et al* do not teach the particular liver-specific enhancer.

ILL et al teach that certain viral cis-acting post-transcriptional regulatory element could enhance expression of intronless genes by facilitating the export of the gene transcript from the nucleus into the cytoplasm of the cell (abstract). In a preferred embodiment, they disclose a liver-specific enhancer (SEQ ID No: 1) having 95.3% sequence homology with 150-278 of instant SEQ ID No: 1 operably linked with a B-domain deleted FVIII and expressing such *in vivo* at therapeutic levels (Fig. 6).

Although *ILL et al* do not teach the claimed AAV vector, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the vector and the expression control elements taught by *Dwarki et al, Ill et al, and Robbins et al* in expressing a B-domain-deleted FVIII with a reasonable expectation of

success. The ordinary skilled artisan would have been motivated to modify the claimed vector because it is known that an AAV is more efficient in cell entry and sustained expression compared to the plasmid taught by *Ill et al*, and the enhancer used by *Ill et al* has proven efficient in expressing B-domain deleted FVIII. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 2 and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Dwarki et al* (US 6,221,349), *Robbins* (Pharmacol Ther 1998;80:35-47), and *Pittman et al* (Blood 1993;81:2925-35) as applied to claims 1, 3-11, 13-18, 20, 58-77, 79-88, and 90-92 above, and further in view of *Gao et al* (US 6,258,595).

In paper #18, applicants argue that Gao et al do not teach that B-domain-deleted FVIII could be expressed at levels sufficient for treatment using a rAAV vector.

In response, it is the combined teachings that illustrate the levels of the skilled in the art, and what the combined teachings of the references would have suggested to those of ordinary skill in the art.

For reasons of record and set forth above, the rejection stands.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-

1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
June 2, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER